Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	78	Hagstrom james	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/01/14 14:27
L2	59	l1 and vector	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/01/14 15:03
L3	10	mirus inc	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/01/14 14:40
L4	6208	intra (vascular OR venous OR arter$4 OR vein)	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/01/14 15:06
L5	47482	gene therapy	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/01/14 15:06
L6	1330	l4 and l5	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/01/14 15:06
L7	1227	l6 AND (viral OR virus)	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/01/14 15:07
L8	269	l6 AND (viral OR virus).clm.	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/01/14 15:11
L9	50	Isolated Limb Perfusion	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/01/14 16:13
L11	30	s l9 l5	US-PGPUB; USPAT; EPO; JPO; DERWENT	AND	ON	2005/01/14 15:21
L12	2	("6177403").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2005/01/14 16:09
L13	3	Isolated Limb Perfusion.clm.	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/01/14 15:24

L14	5	stedman hansell	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/01/14 15:26
L15	4796	vascular permeability	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/01/14 16:08
L16	202	l4 and l15	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/01/14 16:11
L17	54	isolating circulatory system	US-PGPUB; USPAT; EPO; JPO; DERWENT	WITH	ON	2005/01/14 16:10
L21	76	l16 AND l7	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/01/14 16:11
L22	6	l9 AND l15	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/01/14 16:13

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     (FILE 'HOME' ENTERED AT 16:20:04 ON 14 JAN 2005)

     FILE 'MEDLINE, SCISEARCH, CAPLUS, MEDICONF' ENTERED AT 16:20:19 ON 14 JAN
     2005
L1          2154 S ISOLATED (L) LIMB (L) PERFUS?
L2         88619 S GENE THERAPY
L3        405396 S PERMEAB?
L4             0 S L1 (L) L2 (L) L3
L5            26 S L1 (L) L2
L6            14 DUP REM L5 (12 DUPLICATES REMOVED)
L7            14 SORT L6 PY
L8            70 S L1 (L) GENE
L9            39 DUP REM L8 (31 DUPLICATES REMOVED)
L10           14 S L9 AND (VECTOR OR VIRUS OR VIRAL)
L11           14 SORT L10 PY
                 E HAGSTROM JAMES?/AU
                 E HAGSTROM J?/AU
                 E HERWEIJER H?/AU
L12           34 S E4
L13           58 S E2
L14           92 S L12 OR L13
L15           49 DUP REM L14 (43 DUPLICATES REMOVED)
L16           14 S L15 AND L2
L17           14 SORT L16 PY
                 E STEDMAN H?/AU
L18           22 S E6
L19           17 S L18 AND GENE
L20           15 DUP REM L19 (2 DUPLICATES REMOVED)
L21           15 SORT L20 PY

=> d an ti so au ab pi l21 8

L21  ANSWER 8 OF 15  CAPLUS  COPYRIGHT 2005 ACS on STN
AN   1999:425735  CAPLUS
DN   131:63514
TI   Transvascular delivery of a composition to an extravascular tissue of a
     mammal
SO   PCT Int. Appl., 138 pp.
     CODEN: PIXXD2
IN   Stedman, Hansell H.; Bridges, Charles R.
AB   Compns., methods, kits and apparatus are provided for delivering a macromol.
     assembly such as a plasmid, virus vector, or other gene vector,
     to an extravascular tissue such as muscle tissue.  The composition comprises
     the macromol. assembly and a vascular permeability-enhancing agent.  In
     another embodiment, the composition further comprises a vasodilating agent.
     The method of the invention comprises proving a vascular
     permeability-enhancing agent to a blood vessel and providing a macromol.
     assembly to the vessel.  An oxygenator useful for providing oxygen to a
     fluid extracorporeally prior to providing the fluid to a blood vessel of a
     mammal is included in the invention.  Kits, apparatus, and methods for using
     the catheters described herein for isolating cardiac circulation,
     diverting caval blood flow from the right atrium, and other purposes, are
     also described.
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     --------------      ----   --------    -------------------    --------
PI   WO 9931982           A1     19990701    WO 1998-US27072        19981218
         W:  AU, CA, JP, US
         RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE
     CA 2314905           AA     19990701    CA 1998-2314905        19981218
     AU 9922013           A1     19990712    AU 1999-22013          19981218
     AU 774299            B2     20040624
     EP 1041882           A1     20001011    EP 1998-966022         19981218
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI
     JP 2001526071        T2     20011218    JP 2000-524995         19981218
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US 6673039 B1 20040106 US 2000-597890 20000619

=> d an ti so au ab pi l17 2 7 9

L17 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:534397 CAPLUS
DN 122:281146
TI Direct gene transfer in vivo
SO Somatic Gene Ther. (1995), 183-202. Editor(s): Chang, Patricia L. Publisher: CRC, Boca Raton, Fla.
CODEN: 61EAAZ
AU **Herweijer, Hans**; Fritz, Jeffery D.; Hagstrom, James E.; Wolff, Jon A.
AB A review, with 76 refs. discussing gene transfer techniques such as direct injection of naked DNA, injection of complexed DNA, and direct injection of recombinant viruses.

L17 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:764633 CAPLUS
DN 132:261114
TI Intravascular delivery of naked plasmid DNA
SO Drug Targeting and Delivery (1999), 10(Advanced Gene Delivery), 235-251
CODEN: DTDEET; ISSN: 1058-241X
AU Lockie, Tim; **Herweijer, Hans**; Zhang, Guofeng; Budker, Vladimir; Wolff, Jon A.
AB A review with 113 refs. outlining the new methods that have been explored to deliver plasmid DNA to tissues using an intravascular route. The interstitial and intravascular delivery of plasmid DNA to muscles and liver are emphasized.

L17 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:751380 CAPLUS
DN 137:268411
TI Nucleic acid transfer complexes
SO U.S., 19 pp.
CODEN: USXXAM
IN **Herweijer, Hans**; Budker, Vladimir G.
AB The present invention relates to compns. and methods for transferring nucleic acids into cells in vitro and in vivo. The compns. comprise a transfection reagent and one or more detergents. In preferred embodiments, the compns. comprise delivery systems providing nucleic acid transfer complexes that transfect cells with high efficiency.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6458382	B1	20021001	US 2000-709656	20001110
	US 2003044983	A1	20030306	US 2002-161241	20020531

=> d an ti so au ab l11 5 6 8

L11 ANSWER 5 OF 14 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AN 1999:965020 SCISEARCH
TI **Gene** therapy by **isolated limb** **perfusion** results in high local transfection and is the only modality capable of inducing tumor response with an adeno **virus** IL-3 construct.
SO CLINICAL CANCER RESEARCH, (NOV 1999) Vol. 5, Supp. [S], pp. 393-393. Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202. ISSN: 1078-0432.
AU deWilt J H W (Reprint); tenHagen T L M; Eggermont A M M; Bout A; deRoos W K; Valerio D; vanderKaaden M E

L11 ANSWER 6 OF 14 MEDLINE on STN
AN 2001050853 MEDLINE
TI **Isolated limb perfusion** for local **gene** delivery: efficient and targeted adenovirus-mediated **gene** transfer into soft tissue sarcomas.
SO Annals of surgery, (2000 Dec) 232 (6) 814-21. Journal code: 0372354. ISSN: 0003-4932.
AU de Roos W K; de Wilt J H; van Der Kaaden M E; Manusama E R; de Vries M W; Bout A; ten Hagen T L; Valerio D; Eggermont A M
AB OBJECTIVE: To evaluate the potential of **isolated limb** **perfusion** (ILP) for efficient and tumor-specific adenovirus-mediated **gene** transfer in sarcoma-bearing rats. SUMMARY BACKGROUND DATA: A major concern in adenovirus-mediated **gene** therapy in cancer is the transfer of **genes** to organs other than the tumor, especially organs with a rapid cell turnover. Adjustment of the **vector** delivery route might be an option creating tumor specificity in therapeutic **gene** expression. METHODS: Rat hind **limb** sarcomas (5-10 mm) were transfected with recombinant adenoviruses. Intratumoral luciferase expression after ILP was compared with systemic administration, regional infusion, or intratumoral injection using a similar dose of adenoviruses carrying the luciferase marker **gene**. Localization studies using lacZ as a marker **gene** were performed to evaluate the intratumoral distribution of transfected cells after both ILP and intratumoral injection. RESULTS: Intratumoral luciferase activity after ILP or intratumoral administration was significantly higher compared with regional infusion or systemic administration. After ILP, luciferase **gene** expression was minimal in extratumoral organs, whether outside or inside the **isolated** circuit. Localization studies demonstrated that transfection was confined to tumor cells lying along the needle track after intratumoral injection, whereas after ILP, lacZ expression was found in viable tumor cells and in the tumor-associated vasculature. CONCLUSIONS: Using ILP, efficient and tumor-specific **gene** transfection can be achieved. The ILP technique might be useful for the delivery of recombinant adenoviruses carrying therapeutic **gene** constructs to enhance tumor control.

L11 ANSWER 8 OF 14 MEDLINE on STN
AN 2001169689 MEDLINE
TI Adenovirus-mediated interleukin 3 beta **gene** transfer by **isolated limb perfusion** inhibits growth of **limb** sarcoma in rats.
SO Human gene therapy, (2001 Mar 20) 12 (5) 489-502. Journal code: 9008950. ISSN: 1043-0342.
AU de Wilt J H; Bout A; Eggermont A M; van Tiel S T; de Vries M W; ten Hagen T L; de Roos W K; Valerio D; van der Kaaden M E
AB Cytokine **gene** transfer using (multiple) intratumoral injections can induce tumor regression in several animal models, but this administration technique limits the use for human **gene** therapy. In the present studies we describe tumor growth inhibition of established **limb** sarcomas after a single **isolated limb** **perfusion** (ILP) with recombinant adenoviral **vectors** harboring the rat IL-3 beta **gene** (IG.Ad.CMV.rIL-3 beta). In

contrast, a single intratumoral injection or intravenous administration did not affect tumor growth. Dose-finding studies demonstrated a dose-dependent response with a loss of antitumor effect below 1 x 10(9) IU of IG.Ad.CMV.rIL-3 beta. **Perfusions** with adenoviral **vectors** bearing a weaker promoter (MLP promoter) driving the rIL-3 beta **gene** did not result in antitumor responses, suggesting that the rIL-3 beta-mediated antitumor effect depends on the amount of rIL-3 beta protein expressed by the infected cells. Furthermore, it was shown by direct comparison that ILP with IG.Ad.CMV.rIL-3 beta in the ROS-1 osteosarcoma model is at least as efficient as the established therapy with the combination of TNF-alpha and melphalan. Treatment with IG.Ad.CMV.rIL-3 beta induced a transient dose-dependent leukocytosis accompanied by an increase in peripheral blood levels of histamine. Leukocyte infiltrations were also histopathologically demonstrated in tumors after **perfusion**. These results demonstrate that ILP with recombinant adenoviral **vectors** carrying the IL-3 beta transgene inhibits tumor growth in rats and suggest that cytokine **gene** therapy using this administration technique might be beneficial for clinical cancer treatment.

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L7 ANSWER 4 OF 14 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AN 1999:965020 SCISEARCH
TI **Gene therapy** by **isolated limb perfusion** results in high local transfection and is the only modality capable of inducing tumor response with an adeno virus IL-3 construct.
SO CLINICAL CANCER RESEARCH, (NOV 1999) Vol. 5, Supp. [S], pp. 393-393. Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202. ISSN: 1078-0432.
AU deWilt J H W (Reprint); tenHagen T L M; Eggermont A M M; Bout A; deRoos W K; Valerio D; vanderKaaden M E

L7 ANSWER 5 OF 14 MEDLINE on STN
AN 2001050853 MEDLINE
TI Isolated limb perfusion for local gene delivery: efficient and targeted adenovirus-mediated gene transfer into soft tissue sarcomas.
SO Annals of surgery, (2000 Dec) 232 (6) 814-21. Journal code: 0372354. ISSN: 0003-4932.
AU de Roos W K; de Wilt J H; van Der Kaaden M E; Manusama E R; de Vries M W; Bout A; ten Hagen T L; Valerio D; Eggermont A M
AB OBJECTIVE: To evaluate the potential of **isolated limb perfusion** (ILP) for efficient and tumor-specific adenovirus-mediated gene transfer in sarcoma-bearing rats. SUMMARY BACKGROUND DATA: A major concern in adenovirus-mediated **gene therapy** in cancer is the transfer of genes to organs other than the tumor, especially organs with a rapid cell turnover. Adjustment of the vector delivery route might be an option creating tumor specificity in therapeutic gene expression. METHODS: Rat hind **limb** sarcomas (5-10 mm) were transfected with recombinant adenoviruses. Intratumoral luciferase expression after ILP was compared with systemic administration, regional infusion, or intratumoral injection using a similar dose of adenoviruses carrying the luciferase marker gene. Localization studies using lacZ as a marker gene were performed to evaluate the intratumoral distribution of transfected cells after both ILP and intratumoral injection. RESULTS: Intratumoral luciferase activity after ILP or intratumoral administration was significantly higher compared with regional infusion or systemic administration. After ILP, luciferase gene expression was minimal in extratumoral organs, whether outside or inside the **isolated** circuit. Localization studies demonstrated that transfection was confined to tumor cells lying along the needle track after intratumoral injection, whereas after ILP, lacZ expression was found in viable tumor cells and in the tumor-associated vasculature. CONCLUSIONS: Using ILP, efficient and tumor-specific gene transfection can be achieved. The ILP technique might be useful for the delivery of recombinant adenoviruses carrying therapeutic gene constructs to enhance tumor control.

L11 ANSWER 1 OF 14 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN

AN 96:301283 SCISEARCH

TI ADENOVIRAL GENE-TRANSFER - AN ALTERNATIVE IMMUNOTHERAPY IN PERIPHERAL XENOTRANSPLANTATION

SO LANGENBECKS ARCHIV FUR CHIRURGIE, (1996) Supp. 1, pp. 61-65. ISSN: 0023-8236.

AU HEBEBRAND D (Reprint); DRAZAN K; JONES N F; STEINAU H U

AB In this model of **isolated limb perfusion** the persistence and distribution of adenoviral **vectors** were evaluated. Following **perfusion** for 90 minutes in muscle tissue intensity of **gene** expression of a beta-galaktosidase marker **gene** was found to be highest after 48 hours. The persistence of the **gene** could be shown for 21 days. Although nerve tissues demonstrated a lower transfection rate there were still 79% positive for the control **vector**. The widespread of **gene** expression could be shown in all tissues with a maximum in and around the vessles. The insertion of sequences in the vascular system and muscles by adenoviral **vectors** encoding for immunomodulating cytokines, inhibitory proteins or monoclonal antibodies might improve the results of xenotransplantation.

L11 ANSWER 10 OF 14 MEDLINE on STN
AN 2003340207 MEDLINE
TI Current uses of isolated limb perfusion in the clinic and a model system for new strategies.
SO lancet oncology, (2003 Jul) 4 (7) 429-37. Ref: 75
Journal code: 100957246. ISSN: 1470-2045.
AU Eggermont Alexander M M; de Wilt Johannes H W; ten Hagen Timo L M
AB **Isolated limb perfusion** with melphalan is the treatment of choice for multiple (small) melanoma-in-transit metastases. The use of tumour necrosis factor alpha (TNFalpha) in **isolated limb perfusion** is successful for treatment of locally advanced **limb** soft-tissue sarcomas and other large tumours; this approach can avoid the need for amputation. TNFalpha was approved in Europe after a multicentre trial in patients with locally advanced soft-tissue sarcomas, deemed unresectable by an independent review committee; the response rate to **isolated limb perfusion** with TNFalpha plus melphalan was 76% and the **limb** was saved in 71% of patients. Moreover, the trial showed the efficacy of **isolated limb perfusion** of TNFalpha and melphalan against various other **limb**-threatening tumours such as skin cancers and drug-resistant bony sarcomas. Laboratory models of **isolated limb perfusion** have helped to elucidate mechanisms of action and to develop new treatment modalities. They have identified TNFalpha-mediated vasculotoxic effects on the tumour vasculature and have shown that addition of TNFalpha to the **perfusate** results in an increase of three to six times in uptake of melphalan or doxorubicin by tumours. New vasoactive drugs and new mechanisms of action are being discovered. Moreover, **isolated limb perfusion** is an effective modality for **gene** therapy mediated by an adenoviral **vector**. Various clinical phase I-II studies can be expected in the next few years.

L7 ANSWER 2 OF 14 MEDLINE on STN
AN 1999111173 MEDLINE
TI Isolated limb perfusion in the sarcoma-bearing rat: a novel preclinical gene delivery system.
SO Clinical cancer research : an official journal of the American Association for Cancer Research, (1997 Dec) 3 (12 Pt 1) 2197-203.
Journal code: 9502500. ISSN: 1078-0432.
AU Milas M; Feig B; Yu D; Oriuchi N; Cromeens D; Ge T; Wong F C; Kim E E; Pollock R
AB Reliable site-specific delivery of genetic constructs remains a challenging component of gene-based therapy of solid tumors. **Isolated limb perfusion** (ILP) continues to be evaluated for treatment of locally advanced soft tissue sarcomas because this approach uniquely directs therapeutic agents into the tumor-bearing extremity without significant systemic leak. In light of these considerations, we tested the hypothesis that ILP could be used to deliver genes carried in viral vectors to the sarcoma-bearing rat extremity, resulting in demonstrable gene transfer into the tumor. ILP was performed in rats by cannulating the femoral artery and vein, isolating the hind **limb** from systemic circulation by tourniquet, and cycling **perfusate** for 15 min at a rate of 2.4 ml/min. Leakage into the systemic circulation was 7.5% of the total **perfusate** concentrated in the **isolated limb**, as determined by **perfusion** with technetium 99m-tagged RBCs. We used the ILP technique to **perfuse** rat hind **limbs** bearing syngeneic fibrosarcoma tumor nodules with the replication-defective adenovirus Ad5LacZ, which expresses the bacterial beta-galactosidase. 5-Bromo-4-chloro-3-indolyl-beta-D-galactoside staining of the **perfused limb** tissues confirmed gene transfer to the tumor and peritumoral tissue, demonstrating that the tumor was part of the **perfusion** circuit and that **gene therapy** delivered via this method was feasible. These results suggest that adaptation of this preclinical gene delivery model to administer genetic constructs aimed at controlling tumor growth may prove beneficial to patients with extremity sarcomas.

Field: **Author**

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Items 1 - 5 of 5 One

1: Hagstrom JE, Hegge J, Zhang G, Noble M, Budker V, Lewis DL, Herweijer H, Wolff JA. Related Articles

A facile nonviral method for delivering genes and siRNAs to skeletal muscle mammalian limbs.
Mol Ther. 2004 Aug;10(2):386-98.
PMID: 15294185 [PubMed - in process]

2: Hagstrom JE. Related Articles

Plasmid-based gene delivery to target tissues in vivo: the intravascular appro
Curr Opin Mol Ther. 2003 Aug;5(4):338-44. Review.
PMID: 14513675 [PubMed - indexed for MEDLINE]

3: Slattum PS, Loomis AG, Machnik KJ, Watt MA, Duzeski JL, Budker VG, Wolff JA, Hagstrom JE. Related Articles

Efficient in vitro and in vivo expression of covalently modified plasmid DN
Mol Ther. 2003 Aug;8(2):255-63.
PMID: 12907148 [PubMed - indexed for MEDLINE]

4: Trubetskoy VS, Wong SC, Subbotin V, Budker VG, Loomis A, Hagstrom JE, Wolff JA. Related Articles

Recharging cationic DNA complexes with highly charged polyanions for in and in vivo gene delivery.
Gene Ther. 2003 Feb;10(3):261-71.
PMID: 12571634 [PubMed - indexed for MEDLINE]

5: Hagstrom JE. Related Articles

Self-assembling complexes for in vivo gene delivery.
Curr Opin Mol Ther. 2000 Apr;2(2):143-9. Review.
PMID: 11249634 [PubMed - indexed for MEDLINE]

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